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(17376 BOT)

PATENT

In the specification:

Please amend Tables 1 and 2 on pages 19 to 21 to read as follows:

-- TABLE 1

N-glycosylation:

173-NLTR (SEQ ID NO: 1)
382-NYTI (SEQ ID NO: 2)
411-NFTK (SEQ ID NO: 3)
417-NFTG (SEQ ID NO: 4)

Casein kinase II (CK-2) phosphorylation sites:

51-TNPE (SEQ ID NO: 5)
70-SYYD (SEQ ID NO: 6)
79-TDNE (SEQ ID NO: 7)
120-STID (SEQ ID NO: 8)
253-SGLE (SEQ ID NO: 9)
258-SFEE (SEQ ID.NO: 10)
275-SLQE (SEQ ID NO: 11)
384-TIYD (SEQ ID NO: 12)

N-terminal myristylation sites:

15-GVDIAY (SEQ ID NO: 13)
141-GSYRSE (SEQ ID NO: 14)
254-GLEVSF (SEQ ID NO: 15)

Protein kinase C (PKC) phosphorylation sites:

142-SYR (SEQ ID NO: 16)
327-SGK (SEQ ID NO: 17)

435-TSK (SEQ ID NO: 18)

Tyrosine phosphorylation sites:

92-KLFERIY (SEQ ID NO: 19)

334-KLKFDKLY (SEQ ID NO: 20)

N-glycosylation:

97-NLSG (SEQ ID NO: 21)

138-NGSG (SEQ ID NO: 22)

161-NSSN (SEQ ID NO: 23)

164-NISL (SEQ ID NO: 24)

365-NDSI (SEQ ID NO: 25)

370-NISE (SEQ ID NO: 26)

TABLE 2

Casein kinase II (CK-2) phosphorylation sites:

51-TPQD (SEQ ID NO: 27)

67-SYYD (SEQ ID NO: 28)

76-SDEE (SEQ ID NO: 29)

130-SAVE (SEQ ID NO: 30)

198-SMNE (SEQ ID NO: 31)

247-TNIE (SEQ ID NO: 32)

333-SFTE (SEQ ID NO: 33)

335-TEFD (SEQ ID NO: 34)

N-terminal myristylation sites:

220-GLYGAK (SEQ ID NO: 35)

257-GTDLNI (SEQ ID NO: 36)

386-GQNANL (SEQ ID NO: 37)

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Protein kinase C (PKC) phosphorylation sites:

60-SLK (SEQ ID NO: 38)
166-SLR (SEQ ID NO: 39)
191-SFR (SEQ ID NO: 40)
228-TTK (SEQ ID NO: 41)
234-TQK (SEQ ID NO: 42)
400-TGR (SEQ ID NO: 43)
417-SVK (SEQ ID NO: 44)

Tyrosine kinase phosphorylation sites:

62-KNGDSSY (SEQ ID NO: 45)
300-KDVFEAKY (SEQ ID NO: 46) --

On page 22, please replace the paragraph starting with line 5 with the following paragraph:

-- In one broad embodiment, the modified neurotoxin may include additional modification sites fused onto neurotoxins to form modified neurotoxins. The modification sites may be any modification sites known in the art, including the ones listed on Tables 1 and 2. In one embodiment, such inclusion of the modification site may enhance the biological persistence of the modified neurotoxin. Preferably, the modification site enhances the biological half-life of the modified neurotoxin. More preferably, the biological half-life of the modified neurotoxin is enhanced by about 10%. Even more preferably, the biological half-life of the modified neurotoxin is enhanced by about 100%. Generally speaking, the modified neurotoxin has a biological persistence of about 20% to 300% more than an identical neurotoxin without the structural modification. That is, for example, the modified neurotoxin including the modified site is able to cause a substantial inhibition of acetylcholine release from a nerve terminal for

about 20% to about 300% longer than a neurotoxin that is not modified. A non-limiting example of a modified neurotoxin with an additional modification site is Bo/E with a casein kinase II phosphorylation site, preferably TDNE (SEQ ID NO: 7), fused to its primary structure. More preferably, the TDNE (SEQ ID NO: 7) is fused to position 79 of BoNT/E or a position on BoNT/E which substantially corresponds to position 79 of BoNT/A. --

Please replace the paragraph on page 33, starting on line 33, with the following:

-- A patient, age 39, experiencing pain subsequent to spinal cord injury is treated by intrathecal administration, for example by spinal tap or by catherization (for infusion), to the spinal cord, with about 0.1 U/kg to about 10 U/kg of the modified neurotoxin, preferably the modified neurotoxin comprises BoNT/E with an N-terminal myristylation site, for example GVDIAY (SEQ ID NO: 13), fused to position 15 of its light chain, or a position substantially corresponding to position 15 of the BoNT/A light chain. The particular toxin dose and site of injection, as well as the frequency of toxin administrations depend upon a variety of factors within the skill of the treating physician, as previously set forth. Within about 1 to about 7 days after the modified neurotoxin administration, the patient's pain is substantially reduced. The pain alleviation persists for up to 27 months. --

Please replace the paragraph on page 34, starting on line 24, with the following:

-- A 46 year old woman presents a shoulder-hand syndrome type pain. The pain is particularly localized at the deltoid region. The patient is treated by a bolus injection of about 0.05 U/kg to about 2 U/kg of a modified neurotoxin subcutaneously to the shoulder, preferably the modified neurotoxin comprises BoNT/E with an N-terminal myristylation site, for example GVDIAY (SEQ ID NO: 13), fused to position 15 of its light chain, or a position substantially corresponding to position 15 of the BoNT/A light chain. The particular dose as well as the frequency of administrations depends upon a variety of factors within the skill of the treating physician, as previously set forth. Within

1-7 days after modified neurotoxin administration the patient's pain is substantially alleviated. The duration of the pain alleviation is from about 7 to about 27 months.--

Please replace the paragraph on page 37, starting with line 10 with the following paragraph:

– A male, age 65, with excessive unilateral sweating is treated by administering 0.05 U/kg to about 2 U/kg of a modified neurotoxin, depending upon degree of desired effect. Preferably the modified neurotoxin comprises BoNT/E with an N-terminal myristylation site, for example GVDIAY (SEQ ID NO: 13), fused to position 15 of its light chain, or a position substantially corresponding to position 15 of the BoNT/A light chain. The administration is to the gland nerve plexus, ganglion, spinal cord or central nervous system. The specific site of administration is to be determined by the physician's knowledge of the anatomy and physiology of the target glands and secretary cells. In addition, the appropriate spinal cord level or brain area can be injected with the toxin. The cessation of excessive sweating after the modified neurotoxin treatment is up to 27 months.